

CLAIMS

1. A variant Hepatitis B Virus (HBV) comprising a surface component exhibiting an altered immunological profile compared to a reference HBV.
2. A variant HBV according to claim 1 wherein the surface component on the variant is a surface antigen which comprises a single or multiple amino acid substitution, addition and/or deletion or truncation compared to a surface antigen from said reference HBV and wherein an antibody generated to the reference surface antigen from the reference HBV exhibits reduced capacity for neutralizing said variant HBV.
3. A variant HBV according to claim 2 wherein the surface antigen on the variant comprises an amino acid substitution, addition and/or deletion or truncation compared to the amino acid sequence set forth below:

M X₁ X₂ X₃ X₄ S G X₅ L X₆ P L X₇ V L Q A X₈ X₉ F X₁₀ L T X₁₁ I X₁₂ X₁₃ I P
X₁₄ S L X₁₅ S W W T S L N F L G X₁₆ X₁₇ X₁₈ X₁₉ C X₂₀ G X₂₁ N X₂₂ Q S
X₂₃ X₂₄ S X₂₅ H X₂₆ P X₂₇ X₂₈ C P P X₂₉ C X₃₀ G Y R W M C L X₃₁ R F I I
F L X₃₂ I L L L C L I F L L V L L D X₃₃ Q G M L X₃₄ V C P L X₃₅ P X₃₆ X₃₇
X₃₈ T T S X₃₉ X₄₀ X₄₁ C X₄₂ T C X₄₃ X₄₄ X₄₅ X₄₆ Q G X₄₇ S X₄₈ X₄₉ P X₅₀ X₅₁
C C X₅₂ K P X₅₃ X₅₄ G N C T C I P I P S X₅₅ W A X₅₆ X₅₇ X₅₈ X₅₉ L W E
X₆₀ X₆₁ S X₆₂ R X₆₃ S W L X₆₄ L L X₆₅ X₆₆ F V Q X₆₇ X₆₈ X₆₉ X₇₀ L X₇₁ P X₇₂ V
W X₇₃ X₇₄ X₇₅ I W X₇₆ X₇₇ W X₇₈ W X₇₉ P X₈₀ X₈₁ X₈₂ X₈₃ I X₈₄ X₈₅ P F X₈₆
P L L P I F X₈₇ X₈₈ L X₈₉ X₉₀ X₉₁ I [Formula I];

wherein:

X₁ is E or G or D;

X₂ is N or S or K;

X₃ is I or T;

X₄ is T or A;
X₅ is F or L;
X₆ is G or R;
X₇ is L or R;
X₈ is G or V;
X₉ is F or C;
X₁₀ is L or S or W;
X₁₁ is R or K;
X₁₂ is L or R;
X₁₃ is T or K;
X₁₄ is Q or K;
X₁₅ is D or H;
X₁₆ is G or E or A;
X₁₇ is S or A or V or T or L;
X₁₈ is P or T;
X₁₉ is V or R or T or K or G;
X₂₀ is L or P;
X₂₁ is Q or L or K;
X₂₂ is S or L;
X₂₃ is P or Q;
X₂₄ is T or I;
X₂₅ is N or S;
X₂₆ is S or L;
X₂₇ is T or I;
X₂₈ is S or C;
X₂₉ is I or T;
X₃₀ is P or A;

X₃₁ is R or Q;
X₃₂ is F or C;
X₃₃ is Y or C;
X₃₄ is P or H or S;
X₃₅ is I or L;
X₃₆ is G or R;
X₃₇ is S or T;
X₃₈ is T or S;
X₃₉ is T or V or A;
X₄₀ is G or E or Q;
X₄₁ is P or A or S;
X₄₂ is K or R;
X₄₃ is T or M;
X₄₄ is T or I or S or A;
X₄₅ is P or T or A or I or L;
X₄₆ is A or V;
X₄₇ is N or T;
X₄₈ is M or K or L;
X₄₉ is F or Y or I;
X₅₀ is S or Y;
X₅₁ is C or S;
X₅₂ is T or I or S;
X₅₃ is T or S;
X₅₄ is D or A;
X₅₅ is S or T;
X₅₆ is F or L;
X₅₇ is A or G or V;

X₅₈ is K or R or T;
X₅₉ is Y or F;
X₆₀ is W or G;
X₆₁ is A or G;
X₆₂ is V or A;
X₆₃ is F or L;
X₆₄ is S or N;
X₆₅ is V or A;
X₆₆ is P or Q;
X₆₇ is W or C or S;
X₆₈ is F or C;
X₆₉ is V or D or A;
X₇₀ is G or E;
X₇₁ is S or F;
X₇₂ is T or I;
X₇₃ is L or P;
X₇₄ is S or L;
X₇₅ is A or V;
X₇₆ is M or I;
X₇₇ is M or I;
X₇₈ is Y or F;
X₇₉ is G or E;
X₈₀ is S or N or K;
X₈₁ is L or Q;
X₈₂ is Y or F or H or C;
X₈₃ is S or G or N or D or T;
X₈₄ is V or L;

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X_{85} is S or N;
 X_{86} is I or M or L;
 X_{87} is F or C;
 X_{88} is C or Y;
 X_{89} is W or R;
 X_{90} is V or A; and
 X_{91} is Y or I or S;

and wherein the variant HBV is selected for by a nucleotide analogue of HBV DNA polymerase.

4. A variant HBV according to claim 2 wherein the surface antigen on the variant comprises an amino acid substitution, addition and/or deletion or truncation compared to the amino acid sequence setforth below:

M X_1 X_2 X_3 X_4 S G X_5 L X_6 P L X_7 V L Q A X_8 X_9 F X_{10} L T X_{11} I X_{12} X_{13} I P
 X_{14} S L X_{15} S W W T S L N F L G X_{16} X_{17} X_{18} X_{19} C X_{20} G X_{21} N X_{22} Q S
 X_{23} X_{24} S X_{25} H X_{26} P X_{27} X_{28} C P P X_{29} C X_{30} G Y R W M C L X_{31} R F I I
F L X_{32} I L L L C L I F L L V L L D X_{33} Q G M L X_{34} V C P L X_{35} P X_{36} X_{37}
 X_{38} T T S X_{39} X_{40} X_{41} C X_{42} T C X_{43} X_{44} X_{45} X_{46} Q G X_{47} S X_{48} X_{49} P X_{50} X_{51}
C C X_{52} K P X_{53} X_{54} G N C T C I P I P S X_{55} W A X_{56} X_{57} X_{58} X_{59} L W E
 X_{60} X_{61} S X_{62} R X_{63} S W L X_{64} LL X_{65} X_{66} F V Q X_{67} X_{68} X_{69} X_{70} L X_{71} P X_{72} V
W
 X_{73} X_{74} X_{75} I W X_{76} X_{77} W X_{78} W X_{79} P X_{80} X_{81} X_{82} X_{83} I X_{84} X_{85} P F X_{86} P L
L P I F X_{87} X_{88} L X_{89} X_{90} X_{91} I [Formula I];

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wherein:

- X_1 is E or G or D;
- X_2 is N or S or K;
- X_3 is I or T;
- X_4 is T or A;
- X_5 is F or L;
- X_6 is G or R;
- X_7 is L or R;
- X_8 is G or V;
- X_9 is F or C;
- X_{10} is L or S or W;
- X_{11} is R or K;
- X_{12} is L or R;
- X_{13} is T or K;
- X_{14} is Q or K;
- X_{15} is D or H;
- X_{16} is G or E or A;
- X_{17} is S or A or V or T or L;
- X_{18} is P or T;
- X_{19} is V or R or T or K or G;
- X_{20} is L or P;
- X_{21} is Q or L or K;
- X_{22} is S or L;
- X_{23} is P or Q;
- X_{24} is T or I;
- X_{25} is N or S;
- X_{26} is S or L;

X_{27} is T or I;
 X_{28} is S or C;
 X_{29} is I or T;
 X_{30} is P or A;
 X_{31} is R or Q;
 X_{32} is F or C;
 X_{33} is Y or C;
 X_{34} is P or H or S;
 X_{35} is I or L;
 X_{36} is G or R;
 X_{37} is S or T;
 X_{38} is T or S;
 X_{39} is T or V or A;
 X_{40} is G or E or Q;
 X_{41} is P or A or S;
 X_{42} is K or R;
 X_{43} is T or M;
 X_{44} is T or I or S or A;
 X_{45} is P or T or A or I or L;
 X_{46} is A or V;
 X_{47} is N or T;
 X_{48} is M or K or L;
 X_{49} is F or Y or I;
 X_{50} is S or Y;
 X_{51} is C or S;
 X_{52} is T or I or S;
 X_{53} is T or S;

X₅₄ is D or A;
X₅₅ is S or T;
X₅₆ is F or L;
X₅₇ is A or G or V;
X₅₈ is K or R or T;
X₅₉ is Y or F;
X₆₀ is W or G;
X₆₁ is A or G;
X₆₂ is V or A;
X₆₃ is F or L;
X₆₄ is S or N;
X₆₅ is V or A;
X₆₆ is P or Q;
X₆₇ is W or C or S;
X₆₈ is F or C;
X₆₉ is V or D or A;
X₇₀ is G or E;
X₇₁ is S or F;
X₇₂ is T or I;
X₇₃ is L or P;
X₇₄ is S or L;
X₇₅ is A or V;
X₇₆ is M or I;
X₇₇ is M or I;
X₇₈ is Y or F;
X₇₉ is G or E;
X₈₀ is S or N or K;

X₈₁ is L or Q;
X₈₂ is Y or F or H or C;
X₈₃ is S or G or N or D or T;
X₈₄ is V or L;
X₈₅ is S or N;
X₈₆ is I or M or L;
X₈₇ is F or C;
X₈₈ is C or Y;
X₈₉ is W or R;
X₉₀ is V or A; and
X₉₁ is Y or I or S.

and wherein the variant HBV is selected for following immunological therapy directed against a surface antigen as defined in Formula I.

5. A variant HBV according to claim 1 comprising a nucleotide sequence having a single or multiple nucleotide substitution, addition and/or deletion or truncation of the nucleotide sequence as set forth in formula III below:

AC N₁ AAA C C T N₂ N₃ G G A N₄ G G A A A N₅ T G C A C N₆ T G T
A T T C C C A T C C C A T C N₇ T C N₈ T G G G C T T T C G N₉ A A
N₁₀ A T N₁₁ C C T A T G G G A G N₁₂ G G G C C T C A G N₁₃ C C G T
T T C T C N₁₄ T G G C T C A G T T A C T A G T G C C A T T T G T
T C A G T G G T T C G N₁₅ A G G G C T T C C C C A C T G T N₁₆
T G G C T T T C A G N₁₇ T A T A T G G A T G A T G T G G T N₁₈ T T
G G G G G C C A A G T C T G T A C A N₁₉ C A T C N₂₀ T G A G T C C
C T T T N₂₁ T N₂₂ C C N₂₃ C T N₂₄ T T A C C A A T T T C T T N₂₅ T G
T C T N₂₆ T G G G N₂₇ A T A C A T T [Formula III];

wherein:

- N₁ is A or C;
- N₂ is T or A;
- N₃ is C or T;
- N₄ is C or T;
- N₅ is C or T;
- N₆ is C or T;
- N₇ is A or G;
- N₈ is T or C;
- N₉ is C or G;
- N₁₀ is G or A;
- N₁₁ is T or A;
- N₁₂ is T or G;
- N₁₃ is T or C;
- N₁₄ is C or T;
- N₁₅ is T or C;
- N₁₆ is T or C;
- N₁₇ is T or C;
- N₁₈ is A or T;
- N₁₉ is A or G;
- N₂₀ is T or G;
- N₂₁ is A or T;
- N₂₂ is A or G;
- N₂₃ is T or G;
- N₂₄ is A or G;
- N₂₅ is T or C;
- N₂₆ is T or C; and

N_{27} is T or C.

and wherein the HBV variant has a surface antigen exhibiting an altered immunological profile relative to the surface antigen as defined in Formula I.

6. An isolated variant Hepatitis B virus surface antigen (HBsAg) or a recombinant form thereof or a derivative or chemical equivalent thereof wherein said HBsAg or its recombinant or derivative form or its chemical equivalent exhibits an altered immunological profile compared to an HBsAg from a reference HBV.

7. An isolated variant HBsAg or a recombinant or derivative form thereof or a chemical equivalent thereof according to claim 6 wherein the variant HBsAg comprises an amino acid sequence having a single or multiple substitution, addition and/or deletion or truncation of the amino acid sequence set forth below:

M X_1 X_2 X_3 X_4 S G X_5 L X_6 P L X_7 V L Q A X_8 X_9 F X_{10} L T X_{11} I X_{12} X_{13} I P
 X_{14} S L X_{15} S W W T S L N F L G X_{16} X_{17} X_{18} X_{19} C X_{20} G X_{21} N X_{22} Q S
 X_{23} X_{24} S X_{25} H X_{26} P X_{27} X_{28} C P P X_{29} C X_{30} G Y R W M C L X_{31} R F I I
F L X_{32} I L L L C L I F L L V L L D X_{33} Q G M L X_{34} V C P L X_{35} P X_{36} X_{37}
 X_{38} T T S X_{39} X_{40} C X_{41} C X X_{42} T C X_{43} X_{44} X_{45} X_{46} Q G X_{47} S X_{48} X_{49} P X_{50} X_{51}
C C X_{52} K P X_{53} X_{54} G N C T C I P I P S X_{55} W A X_{56} X_{57} X_{58} X_{59} L W E
 X_{60} X_{61} S X_{62} R X_{63} S W L X_{64} LL X_{65} X_{66} F V Q X_{67} X_{68} X_{69} X_{70} L X_{71} P X_{72} V
W
 X_{73} X_{74} X_{75} I W X_{76} X_{77} W X_{78} W X_{79} P X_{80} X_{81} X_{82} X_{83} I X_{84} X_{85} P F X_{86} P L
L P I F X_{87} X_{88} L X_{89} X_{90} X_{91} I [Formula I];

wherein:

X_1 is E or G or D;

X_2 is N or S or K;

X₃ is I or T;
X₄ is T or A;
X₅ is F or L;
X₆ is G or R;
X₇ is L or R;
X₈ is G or V;
X₉ is F or C;
X₁₀ is L or S or W;
X₁₁ is R or K;
X₁₂ is L or R;
X₁₃ is T or K;
X₁₄ is Q or K;
X₁₅ is D or H;
X₁₆ is G or E or A;
X₁₇ is S or A or V or T or L;
X₁₈ is P or T;
X₁₉ is V or R or T or K or G;
X₂₀ is L or P;
X₂₁ is Q or L or K;
X₂₂ is S or L;
X₂₃ is P or Q;
X₂₄ is T or I;
X₂₅ is N or S;
X₂₆ is S or L;
X₂₇ is T or I;
X₂₈ is S or C;
X₂₉ is I or T;

X_{30}	is P or A;
X_{31}	is R or Q;
X_{32}	is F or C;
X_{33}	is Y or C;
X_{34}	is P or H or S;
X_{35}	is I or L;
X_{36}	is G or R;
X_{37}	is S or T;
X_{38}	is T or S;
X_{39}	is T or V or A;
X_{40}	is G or E or Q;
X_{41}	is P or A or S;
X_{42}	is K or R;
X_{43}	is T or M;
X_{44}	is T or I or S or A;
X_{45}	is P or T or A or I or L;
X_{46}	is A or V;
X_{47}	is N or T;
X_{48}	is M or K or L;
X_{49}	is F or Y or I;
X_{50}	is S or Y;
X_{51}	is C or S;
X_{52}	is T or I or S;
X_{53}	is T or S;
X_{54}	is D or A;
X_{55}	is S or T;
X_{56}	is F or L;

X_{57}	is A or G or V;
X_{58}	is K or R or T;
X_{59}	is Y or F;
X_{60}	is W or G;
X_{61}	is A or G;
X_{62}	is V or A;
X_{63}	is F or L;
X_{64}	is S or N;
X_{65}	is V or A;
X_{66}	is P or Q;
X_{67}	is W or C or S;
X_{68}	is F or C;
X_{69}	is V or D or A;
X_{70}	is G or E;
X_{71}	is S or F;
X_{72}	is T or I;
X_{73}	is L or P;
X_{74}	is S or L;
X_{75}	is A or V;
X_{76}	is M or I;
X_{77}	is M or I;
X_{78}	is Y or F;
X_{79}	is G or E;
X_{80}	is S or N or K;
X_{81}	is L or Q;
X_{82}	is Y or F or H or C;
X_{83}	is S or G or N or D or T;

X₈₄ is V or L;
X₈₅ is S or N;
X₈₆ is I or M or L;
X₈₇ is F or C;
X₈₈ is C or Y;
X₈₉ is W or R;
X₉₀ is V or A; and
X₉₁ is Y or I or S;

and wherein a neutralizing antibody directed to a reference HBV exhibits no or reduced neutralizing activity to an HBV carrying said variant HBsAg.

8. An isolated variant HBsAg according to claim 7 encoded by a nucleotide sequence having a single or multiple nucleotide substitution, addition and/or deletion or truncation relative to the nucleotide sequence set forth below:

A C N₁ A A A C C T N₂ N₃ G G A N₄ G G A A A N₅ T G C A C N₆ T G T A
T T C C C A T C C C A T C N₇ T C N₈ T G G G C T T T C G N₉ A A N₁₀ A
T N₁₁ C C T A T G G G A G N₁₂ G G G C C T C A G N₁₃ C C G T T T C T C
N₁₄ T G G C T C A G T T A C T A G T G C C A T T T G T T C A G T G G
T T C G N₁₅ A G G G C T T C C C C A C T G T N₁₆ T G G C T T T C A
G N₁₇ T A T A T G G A T G A T G T G G T N₁₈ T T G G G G G C C A A G
T C T G T A C A N₁₉ C A T C N₂₀ T G A G T C C C T T T N₂₁ T N₂₂ C C N₂₃
C T N₂₄ T T A C C A A T T T C T T N₂₅ T G T C T N₂₆ T G G G N₂₇ A T A
C A T T [FORMULA III];

wherein:

N₁ is A or C;

N₂ is T or A;
N₃ is C or T;
N₄ is C or T;
N₅ is C or T;
N₆ is C or T;
N₇ is A or G;
N₈ is T or C;
N₉ is C or G;
N₁₀ is G or A;
N₁₁ is T or A;
N₁₂ is T or G;
N₁₃ is T or C;
N₁₄ is C or T;
N₁₅ is T or C;
N₁₆ is T or C;
N₁₇ is T or C;
N₁₈ is A or T;
N₁₉ is A or G;
N₂₀ is T or G;
N₂₁ is A or T;
N₂₂ is A or G;
N₂₃ is T or G;
N₂₄ is A or G;
N₂₅ is T or C;
N₂₆ is T or C; and
N₂₇ is T or C.

9. A variant HBV or an isolated HBsAg from said variant HBV wherein said variant HBV comprises an HBsAg having a single or multiple amino acid substitution, addition and/or deletion or truncation relative to the HBsAg on a reference HBV and whereas the HBsAg variant is defined by a single or multiple amino acid substitution, addition and/or truncation to the catalytic region of HBV DNA polymerase as defined below:

S Z₁ L S W L S L D V S A A F Y H Z₂ P L H P A A M P H L L Z₃ G S S
G L Z₄ R Y V A R L S S Z₅ S Z₆ Z₇ X N Z₈ Q Z₉ Z₁₀ X X X Z₁₁ L H Z₁₂ Z₁₃
C S R Z₁₄ L Y V S L Z₁₅ L L Y Z₁₆ T Z₁₇ G Z₁₈ K L H L Z₁₉ Z₂₀ H P I Z₂₁ L
G F R K Z₂₂ P M G Z₂₃ G L S P F L L A Q F T S A I Z₂₄ Z₂₅ Z₂₆ Z₂₇ Z₂₈ R
A F Z₂₉ H C Z₃₀ Z₃₁ F Z₃₂ Y M D D Z₃₃ V L G A Z₃₄ Z₃₅ Z₃₆ Z₃₇ H Z₃₈ E Z₃₉
L Z₄₀ Z₄₁ Z₄₂ Z₄₃ Z₄₄ Z₄₅ Z₄₆ L L Z₄₇ Z₄₈ G I H L N P Z₄₉ K T K R W G Y S
L N F M G Y Z₅₀ I G [Formula II];

wherein:

X is any amino acid;

Z₁ is N or D;

Z₂ is I or P;

Z₃ is I or V;

Z₄ is S or D;

Z₅ is T or N;

Z₆ is R or N;

Z₇ is N or I;

Z₈ is N or Y or H;

Z₉ is H or Y;

Z₁₀ is G or R;

Z₁₁ is D or N;

Z₁₂ is D or N;

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Z_{13} is S or Y;
 Z_{14} is N or Q;
 Z_{15} is L or M;
 Z_{16} is K or Q;
 Z_{17} is Y or F;
 Z_{18} is R or W;
 Z_{19} is Y or L;
 Z_{20} is S or A;
 Z_{21} is I or V;
 Z_{22} is I or L;
 Z_{23} is V or G;
 Z_{24} is C or L;
 Z_{25} is A or S;
 Z_{26} is V or M;
 Z_{27} is V or T;
 Z_{28} is R or C;
 Z_{29} is F or P;
 Z_{30} is L or V;
 Z_{31} is A or V;
 Z_{32} is S or A;
 Z_{33} is V or L or M;
 Z_{34} is K or R;
 Z_{35} is S or T;
 Z_{36} is V or G;
 Z_{37} is Q or E;
 Z_{38} is L or S or R;
 Z_{39} is S or F;

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Z_{40} is F or Y;
 Z_{41} is T or A;
 Z_{42} is A or S;
 Z_{43} is V or I;
 Z_{44} is T or C;
 Z_{45} is N or S;
 Z_{46} is F or V;
 Z_{47} is S or D;
 Z_{48} is L or V;
 Z_{49} is N or Q;
 Z_{50} is V or I; and
M is amino acid 550.

10. A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of G112R, T123P, Y/F134S, D144E, G145R, A157D, E164D, F170L, M195I, W196L, S196W, W196STOP, M198I, W199S, S204T and S210R wherein "STOP" means a stop codon.

11. A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of :
D144E, G145R, A157D, E164D, M195I, W196L, S196W, W196STOP, M198I, W199S and S210R wherein "STOP" means a codon.

12. A variant HBV or variant HBsAg from said variant HBV comprising a mutation selected from the list consisting of:
Q476, N480G, N485K, K495R, R499O, G499E, W499Q, F512L, I515L, V519L, L526M, M550V, M550I, V553I and S565P.

13. A composition comprising a variant HBV or variant HBsAg according to any one of

Sub
A1

- 55 -

*Sub
A1 cont'd*

claims 1 to 12 or a recombinant or derivative form or its chemical equivalent.

14. A composition according to claim 13 further comprising one or more pharmaceutically acceptable carriers and/or diluents.

*Sub
A2*

15. A method for the treatment or prophylaxis of HBV infection said method comprising administering to a subject an amount of a variant HBV or variant HBsAg according to any one of claims 1 to 12 or a composition according to claim 13 or 14, said amount being effective to induce an immune response to said variant HBV.

16. Use of a variant HBV or an HBsAg from said HBV in the manufacture of a medicament for the treatment or prophylaxis of infection by said variant HBV.

17. Use of a variant HBV or an HBsAg from said variant HBV in screening for an agent useful in the treatment or prophylaxis of infection by said variant HBV.